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In patients with proven esophageal hemorrhage, is esophageal ligation still treatment of choice in secondary prophylaxis of variceal bleeding? A comparative literature review

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Abstract

Background: Esophageal bleeding has an estimated mortality rate of at least 25% with the index bleed, an estimated 35% to 42% risk of death within the first six weeks, and up to 75% chance of a rebleed at one year. Prevention of chronic variceal rebleeding is critical and most crucial in the first three months following the index bleed. To address this, several medical and surgical therapies have been studied and used with various levels of success. For several years, esophageal variceal ligation (EVL) has been accepted as the best overall prevention for chronic variceal rebleeding, given the advantages and disadvantages of each treatment method. However, recent trials in pharmacological therapy using beta-blockers, in combination with a nitrate, have shown greater efficacy in preventing recurrent variceal bleeding, studies combining pharmacological and nonpharmacological modalities have been performed, and technological advances have decreased the rebleeding rate after transesophageal intrahepatic portosystemic shunt (TIPS) therapy. This has created the possibility that another treatment may be better than EVL alone. Further study and trials are necessary to determine if esophageal variceal ligation is still the treatment of choice for secondary prevention of variceal rebleeding.

Clinical Question: In patients with proven esophageal hemorrhage, is esophageal ligation still the treatment of choice in secondary prophylaxis of variceal bleeding?

Study Design: Exhaustive search of available medical literature employing CINAHL, MEDLINE, Evidence Based Medicine Reviews Multifile, BIOSIS preview databases. Studies were found in key industry journals, and article reference lists were combed for additional trials meeting inclusion criteria.

Methods: Independent review of data and methodology of published randomized control trials addressing long-term prevention of esophageal variceal bleeding using esophageal variceal ligation as compared to another treatment modality, or as compared to EVL plus another therapy, performed within the last 10 years, and free on internet search.

Results: In reviewing the efficacy of esophageal variceal ligation (EVL) therapy to other modes of treatment for secondary prophylaxis of variceal bleeds, one study showed an improved benefit in variceal rebleeding rate and overall bleeding rate when esophageal variceal ligation was compared to propranolol, a nonselective beta-blocker, plus isosorbide mononitrate (ISMN). In two studies comparing EVL to ISMN plus nadolol, a different nonselective beta-blocker, one study reported no significant difference in rebleeding, overall bleed, or mortality rates and the other trial concluded that EVL was less effective than nadolol plus ISMN and EVL, in isolation, had an associated higher rate of major complications. A fourth trial compared variceal ligation to a combination therapy of EVL plus nadolol and found that nadolol plus EVL reduced the incidence of variceal rebleeding as compared to EVL, but did not reduce the risk of mortality. When evaluated against transesophageal intrahepatic portosystemic shunt (TIPS), EVL proved to be less effective than TIPS, nor did it improve the two-year survival rate or encephalopathy rate. In the final study reviewed, a combination therapy of variceal ligation plus propranolol was found to be nearly as effective as TIPS, and with an equally effective survival rate, but ligation plus propranolol had approximately half the risk of encephalopathy. These randomized controlled trial results showed contradictory evidence for the efficacy of esophageal variceal ligation in the control of secondary variceal rebleeding. Esophageal variceal ligation therapy, alone, did not

show a clear benefit in the long-term prevention of variceal rebleeding as compared to beta-blocker plus nitrate, EVL plus beta-blocker, or TIPS. However, when EVL was paired with a beta-blocker, and pitted against variceal ligation alone, the combination comparatively reduced the incidence of variceal rebleeding.

Conclusion: Esophageal variceal ligation, in isolation, shows no superiority to treatment with beta-blocker and nitrate, or TIPS procedure, and is less effective than EVL plus nadolol in the prevention of secondary variceal bleeding.

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A Clinical Graduate Project Submitted to the Faculty of the

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Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC

Biography

Emily Forsyth is a California native. She majored in Physiology at UC Berkeley, followed by a Bachelors degree in Nursing at Samuel Merritt College. After completion, she moved to Washington and worked for 13 years in OBGYN, orthopedics, allergy/asthma and infectious disease specialties. While raising 2 great children, she has pursued her Master's degree in Physician's Assistant studies and plans to begin a career in Family Medicine.

Abstract

Objective: To review the efficacy of current treatment modalities in comparison to esophageal variceal ligation therapy for the long-term prevention of esophageal variceal rebleeding.

Background: Esophageal bleeding has an estimated mortality rate of at least 25% with the index bleed, an estimated 35% to 42% risk of death within the first six weeks, and up to 75% chance of a rebleed at one year. Prevention of chronic variceal rebleeding is critical and most crucial in the first three months following the index bleed. To address this, several medical and surgical therapies have been studied and used with various levels of success. For several years, esophageal variceal ligation (EVL) has been accepted as the best overall prevention for chronic variceal rebleeding, given the advantages and disadvantages of each treatment method. However, recent trials in pharmacological therapy using beta-blockers, in combination with a nitrate, have shown greater efficacy in preventing recurrent variceal bleeding, studies combining pharmacological and nonpharmacological modalities have been performed, and technological advances have decreased the rebleeding rate after transesophageal intrahepatic portosystemic shunt (TIPS) therapy. This has created the possibility that another treatment may be better than EVL alone. Further study and trials are necessary to determine if esophageal variceal ligation is still the treatment of choice for secondary prevention of variceal rebleeding.

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the incidence of variceal rebleeding as compared to EVL, but did not reduce the risk of mortality. When evaluated against transesophageal intrahepatic portosystemic shunt (TIPS), EVL proved to be less effective than TIPS, nor did it improve the two-year survival rate or encephalopathy rate. In the final study reviewed, a combination therapy of variceal ligation plus propranolol was found to be nearly as effective as TIPS, and with an equally effective survival rate, but ligation plus propranolol had approximately half the risk of encephalopathy.

These randomized controlled trial results showed contradictory evidence for the efficacy of esophageal variceal ligation in the control of secondary variceal rebleeding. Esophageal variceal ligation therapy, alone, did not show a clear benefit in the long-term prevention of variceal rebleeding as compared to beta-blocker plus nitrate, EVL plus beta-blocker, or TIPS. However, when EVL was paired with a beta-blocker, and pitted against variceal ligation alone, the combination comparatively reduced the incidence of variceal rebleeding.

Conclusion: Esophageal variceal ligation, in isolation, shows no superiority to treatment with beta-blocker and nitrate, or TIPS procedure, and is less effective than EVL plus nadolol in the prevention of secondary variceal bleeding.

Keywords: beta-blockers, cirrhotic, EIS, esophageal injection sclerotherapy, esophageal variceal ligation, esophageal varices, EVL, gastrointestinal, octreotide, omeprazole, portal hypertension, prevention, propranolol, prospective, randomized, TIPS, transjugular intrahepatic portosystemic stent, trial, variceal bleeding, varix, vasopressin.

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To *my family and friends*: Thank you for allowing me to pursue this personal goal and for all your unflagging support, your cooking, your listening, through this taxing, albeit rewarding, process.

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List of Abbreviations

Bpm ..... beats per minute

EIS ..... Esophageal injection sclerotherapy

EVL ..... Esophageal variceal ligation

GI ..... gastrointestinal

HVPG ..... hepatic venous pressure gradient

RCT ..... randomized control trial

TIPS ..... transjugular intrahepatic portosystemic shunt

TIPSS ..... transjugular intrahepatic portosystemic stent shunt

VBL ..... variceal band ligation

INTRODUCTION AND BACKGROUND

Many factors may lead to the development of portal hypertension, which is defined by pathological increase in the pressure in the portal venous system.[1] In turn, portal hypertension may be the result of chronic liver injury, and can be cirrhotic or noncirrhotic, in nature.

The main causes of cirrhotic liver disease with elevated portal hypertension are alcoholic cirrhosis, chronic Hepatitis B or Hepatitis C virus, primary biliary cirrhosis, hemochromatosis or Wilson's disease. Cirrhotic liver disease is a late stage development in which there is liver architecture degeneration concomitant with progressive hepatic fibrosis, followed by formation of dysfunctional nodules. As a result of these changes, there occurs the synchronous development of portal hypertension. The continuum of cirrhosis ranges from potential reversibility in its early stages, to ultimately irreversible advanced cirrhosis which has few options for treatment other than hepatic lobectomy or full liver transplant. While in that continuum, one possible life-threatening complication is esophageal variceal hemorrhage, a sign of decompensated liver disease. (Other complications may include ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, hepatopulmonary syndrome, and hepatocellular carcinoma).[2]

The importance of esophageal variceal bleeding, as a major complication of portal hypertension resulting from liver cirrhosis[3], cannot be overstated as it is the leading cause of cirrhosis-related death.[4] Without intervention following a variceal hemorrhage event, approximately 50% of patients will die within three months and mortality is as high as 66% at one year.[5] Even with intervention, 25% of cirrhotic patients presenting with a

major index variceal bleed will die as a result, and for the balance of patients that survive it, there is a 70% chance of rebleeding with a similar mortality.[4] Abid et al state that gastroesophageal varices have been identified in approximately 30% of patients with compensated cirrhosis[6], and the prevalence of esophageal varices that have been identified in patients with liver cirrhosis may range from 60% to 80%.[7] Other research cites esophagogastric varices as responsible for 60%-80% of first bleeds in decompensated cirrhotic patients with portal hypertension.[8] Thus, immediate delivery of efficacious treatment is of vital importance and prevention of rebleed is a major concern.

Noncirrhotic liver disease also may result in acute or chronic variceal bleeding leading to a high morbidity and mortality. Noncirrhotic liver disease with portal hypertension is known by different names around the world. It is called noncirrhotic portal fibrosis (NCPF) in India, and it is known as idiopathic portal hypertension (IPH) in Japan, and seen in this literature search as noncirrhotic portal hypertension (NCPH). We now know that noncirrhotic elevation of portal hypertension is commonly caused by idiopathic portal hypertension (IPH), which exists more in developing countries, and schistosomiasis, which is one of the most common causes of noncirrhotic portal hypertension worldwide[1]. Although the exact mechanisms are, as yet, unknown, factors believed to play a role in the development of idiopathic portal hypertension are recurrent infections, altered immune response, genetic predisposition, hypercoagulability, HIV infection, all leading to increased resistance to portal flow. Liver function is preserved more in NCPH/IPH, as opposed to alcoholic cirrhosis. Thus, while variceal bleeding occurs with IPH, and is the most common clinical presentation of IPH[1], it is generally better tolerated than in cirrhotic liver disease. Patients with IPH may remain

asymptomatic during the early stages of the disease, but histological changes can develop later, engendering symptoms of variceal bleeding, and requiring a subsequent liver transplant. The only form of treatment that cures both the underlying liver disease and the portal hypertension is liver transplantation.[9] All patients with esophageal varices should be evaluated for liver transplantation, however, only a small percentage of the patients live long enough to benefit from this intervention. Thus, whether the diseased state is noncirrhotic or cirrhotic in etiology, there exists the imperative to find the most effective treatment for prevention of secondary variceal bleeding to reduce the life-threatening hemorrhage that may ensue from cirrhotic or noncirrhotic liver disease.

Long-term therapeutic modalities for prevention of esophageal variceal rebleeding are needed after initially gaining control of the index variceal bleed. These treatments may be noninvasive or invasive in nature, or a combination of the two. Recent studies using medical intervention for the prevention of recurrent bleed have included vasoactive drugs, such as nonselective beta blockers, nitrates, and somatostatin analogues. Other nonpharmacological modalities seen commonly in trials for prevention of secondary variceal bleeding include esophageal injection sclerotherapy (EIS), esophageal variceal ligation (EVL), also known as esophageal band ligation (EBL), and transesophageal intrahepatic portosystemic stent (TIPS).

Pharmacological intervention, for the prevention of recurrent variceal bleeding, addresses the development of increased portal pressure, which may lead to the increased likelihood of variceal hemorrhage.[9] The goal of long-term pharmacological therapy then, is to decrease the baseline hepatic venous portal pressure and, thereby, decrease the incidence of variceal bleeding. Nonselective beta blockers can address this problem, but

two issues are persistent: the high rate of nonresponders, regardless of the dose delivered, and the unreliable and variable reduction of portal pressure seen in those who do respond to beta-blockers.[10] By the early 1990s, meta-analysis indicated that beta-blockers were more successful at preventing primary hemorrhage than in preventing recurrent hemorrhage after the index bleed.[9] More recent studies showed that beta-blockers decreased variceal rebleeding by 40% and improved overall survival by 20%, but a high nonresponder rate and contraindications presented problems for its use.[11]

Occurring simultaneously with increased portal hypertension is an increase in portal blood flow, caused by arteriolar splanchnic vasodilatation and hyperkinetic circulation[11]. One vasodilator, 5-isosorbide mononitrate (ISMN), has been used extensively in studies, and has been shown to reduce portal pressure through a decrease in portal blood flow and a decrease in the intrahepatic resistance.[11] Rodríguez-Vilarrupla et al (2007) support this theory, hypothesizing that nitrates probably relax smooth muscle and myofibroblasts.[12] Subsequently, trials using beta blockade augmented with ISMN have been performed and appear to have increased effectiveness when used as secondary prophylaxis for variceal bleeding. Other drugs, such as octreotide, a somatostatin analogue with known inhibitory action on vasodilatory peptide release, also help to mitigate the hyperemic portal response to a recent meal by reducing postprandial hyperemia, thus decreasing the risk of a recurrent variceal bleed.[13] No study comparing variceal ligation with octreotide for prevention of variceal rebleeding was found during this literature search.

Endoscopy, a nonpharmaceutical tool, does not affect the causes of portal hypertension. Thus, both endoscopic injection sclerotherapy (EIS) and endoscopic

variceal ligation (EVL) have short-term effectiveness, with frequent variceal recurrence and rebleeding. EIS controls initial bleeding and prevents further hemorrhage by thrombosing esophageal vessels or thickening the esophageal mucosa over the varix. A sclerosant is injected either directly into the vein (intravariceal) or next to it in the mucosa (paravariceal), or a combination of the two methods. Many variables exist between providers, including type, concentration, and volume of sclerosant, tools used, and technique, thus, EIS results remain somewhat provider-dependent, which may lead to variability in study outcome.[4, 13] Although esophageal injection sclerotherapy is widely used to control variceal bleeding and to eradicate varices to prevent rebleeding, EIS is associated with a rebleeding rate as high as 50% and complications of fever, esophageal ulceration or stricture may occur in up to 40% of patients, and with a mortality rate of one to two percent.[14]

Endoscopic variceal ligation (EVL), an alternative to EIS, is an attractive tool because it results in less variceal rebleeding, and in fewer complications and deaths than injection sclerotherapy.[4] EVL uses small elastic 'O' bands which, when loaded onto the end of the endoscope, may be used to encircle and tie off the varix, leading to tissue necrosis and sloughing. EVL does not use a needle or sclerosant, making it a less invasive therapy than injection sclerotherapy. However, the single band ligators need to be reloaded, taking up precious time during an active bleed, and repeated removal and reinsertion of the tube increases the chance of mucosal tears or hemorrhage, esophageal perforation, and discomfort for the patient. Multiple-band ligators have a suction cup on the end of the endoscope decreasing the visual field by 30%[4] and which may clot with blood during an active bleed, decreasing visibility even more. Total variceal eradication

is achieved more quickly with banding than with EIS[15] and EVL-caused esophageal ulcers are more superficial and resolve more rapidly than EIS-induced ulcers.[4] Bacteremia, appears to occur less often and has a lower rate of associated spontaneous bacterial peritonitis or pneumonia with band ligation treatment as compared to injection sclerotherapy.[4]

Transjugular intrahepatic portosystemic stent (TIPS) shunt is generally used as an emergency treatment for patients who fail endoscopic treatment. The hepatic vein is cannulated via the jugular vein and a tract is opened in the liver tissue to the portal vein, thus decompressing the portal system, thereby, lowering variceal pressure, and hopefully, decreasing the rate of variceal hemorrhage. The procedure does benefit patients with low rebleeding rates, but studies show that rebleeding is common secondary to stent occlusion, and TIPS is associated with an increased risk of encephalopathy.[16]

Invasive portocaval shunt surgery may decrease variceal rebleeding rates but has an associated higher risk of encephalopathy and a greater risk of mortality. No studies were found comparing variceal ligation to portocaval shunt surgery for this review.

METHODS

An electronic search for relevant articles was conducted of available medical literature employing CINAHL, MEDLINE, Evidence Based Medicine Reviews Multifile, BIOSIS preview databases. Search terms in the database review included beta-blockers, bleed, cirrhotic, esophageal injection sclerotherapy, esophageal variceal ligation, esophageal varices, gastrointestinal, octreotide, prevention, propranolol, prospective, randomized, TIPS, transjugular intrahepatic portosystemic stent, trial, varix. Studies

were found in key industry journals, among them Hepatology, Gastroenterology, Gut, Journal of Gastroenterology and Hepatology, Digestive Diseases and Sciences, Annals of Surgery, NEJM, Am J of Gastroenterology, and Endoscopy. Relevant review articles and the bibliographic reference lists were examined for additional sources. Search of the above sources was limited to articles of published studies available on the internet, and available without fee.

Criteria for inclusion were randomized control trials (RCT) or prospective study status performed on cirrhotic and noncirrhotic patients with evidence of esophageal varices. Studies had to address variceal rebleeding rate after therapy as a primary or secondary endpoint. Publication was required within the last 10 years (2000 to 2009) and the studies needed to be available in the English language.

Excluded were patient populations without any history of upper gastrointestinal bleeding or those with a bleeding history other than the index GI bleed, those patients with varices which were deemed "likely to bleed" but had no evidence of prior bleed, and those patients without gastroesophageal varices. Any study published before the year 2000 was excluded from this systematic review.

An independent evaluation was performed by a single individual analyzing data and methodology from the above published randomized control trials or prospective studies which met the inclusion criteria.

RESULTS

This review evaluated six studies regarding the efficacy of esophageal variceal ligation (EVL) therapy in control of variceal rebleeding as compared to other treatment

modalities (see Table I). Three of these studies tested esophageal ligation against a combination pharmacological treatment of beta-blocker plus isosorbide mononitrate, with mixed results, while a fourth study compared EVL to ligation augmented by a beta-blocker and found that ligation alone was not as effective at reducing secondary esophageal bleeding as ligation plus a beta-blocker. The remaining two studies compared EVL, or EVL plus beta-blocker, against transesophageal intrahepatic portosystemic stent therapy. These last two trials found TIPS to be more effective than EVL, but with no increase in mortality rate in the first study, and a recommendation that EVL plus propranolol be used as initial treatment for the prevention of variceal rebleeding in the second. All included studies were randomized and earned a Jadad validity score of three out of five points.

The first three studies reviewed addressed the use of endoscopic variceal ligation versus a pharmacological agent. In a prospective randomized controlled study, Sarin et al., 2005, used propranolol plus isosorbide mononitrate (ISMN) as a comparison. A group of 137 patients with proven esophageal varices as the bleeding source on upper gastrointestinal endoscopy were randomized to receive treatment by endoscopic variceal ligation every 2 weeks until variceal obliteration or until the varix was too small that to be banded. The therapy arm treatment consisted of oral propranolol twice daily, titrated upwards until a 25% decrease in heart rate or 55 bpm, or 240mg/day was reached. After the propranolol dose was stabilized, twice daily oral ISMN was added. Again, the medication dose was titrated upwards until a total dose of ISMN 40mg/day was reached or until side effects precluded further dose elevations. This study, which had a mean follow up of 11.8 months (range 1-40 months), targeted esophageal variceal bleeding as

its primary endpoint. The overall bleeding rate for the EVL arm was reported as 14.1% while the drug treatment arm showed a 27.2% bleed rate (P=0.06) during the study period. When esophageal variceal rebleeding alone was tallied, 5/71 EVL patients (7%) rebled, versus 15/66 patients (22.7%) in the drug therapy arm. "The actuarial probability of bleed at the end of 24 and 36 months was 42% and 66%, respectively, in the drug therapy arm, compared to 33% and 47% in the EVL arm (P= 0.10, log rank test)".[17] When etiology was examined as a possible confounder of variceal bleeding, analysis revealed a cirrhotic bleeding rate of 12.7% and 23.5% in the EVL and drug treatment arms, respectively. However, when the noncirrhotic bleeding rate was calculated, only 4.7% of the patients bled in the EVL arm and a much higher 40% bled in the drug therapy arm of the trial. Bleeding rates calculated according to Child's classification status are also included in this study. (Child's classification, sometimes referred to as Child-Pugh classification, uses serum albumin concentration, bilirubin level, prothrombin time, and the presence of ascites and encephalopathy to measure liver dysfunction level. Child A classification is well compensated liver disease, B class is functionally compromised, and C class is decompensated disease and, thus more likely to have associated variceal bleeding.[21]) In summary, esophageal variceal ligation proved more effective than pharmacological therapy in patients with noncirrhotic portal hypertention (NCPH) but both were equally effective in cirrhotic patients.

Romero et al[15] conducted a randomized controlled trial, published in 2006, using nadolol with ISMN in comparison to EVL. This study followed 109 cirrhotic patients with a recent variceal bleed for a mean follow up period of 17 and 19 months in the nadolol/ISMN and EVL groups, respectively. Fifty-seven patients had 40mg of once

daily oral nadolol titrated upwards until a 25% reduction in heart rate or until a heart rate of 55 bpm was reached. Once this dose was stabilized, twice daily 10mg ISMN was added and titrated up to 40mg/day or until side effects compromised further dosage increase. Treatment failure occurred when patients suffering from side effects to beta-blockers required complete treatment withdrawal. In the esophageal variceal ligation group, ligation banding was performed at 2 week intervals until variceal eradication. Originally, the study design dictated use of a single band ligation device, requiring use of an overtube, but later in the study a multibanding ligation device was used for treatment. When a multiband ligator device was used, no more than 10 bands were placed per session. The two-week EVL interval schedule was changed only if large ulcers or esophageal stenosis was found. Once ligation was complete, one or two sclerotherapy session were given to residual varices. In the pharmacological group, patients were followed every 3 months. The EVL arm patients had endoscopy at one, three, and six month intervals and every six months thereafter. GI and variceal rebleeding events were the primary endpoints. Romero et al.[15] observed no significant difference in esophageal variceal rebleeding rate between nadolol plus ISMN (21/57 patients or 36.8%) and EVL groups (17/52 patients or 32.7%), respectively. Secondary endpoints included survival time and complications. Mortality rate was rated as similar between both groups, i.e., 19.3% versus 19.2% (P=0.9) in the nadolol/ISMN and the EVL groups, respectively. Likewise, other complications were reported as not significantly different between the two groups.[15]

A third study, variceal ligation therapy with a pharmaceutical challenge, was performed by Villanueva et al.[18] Primary endpoints of recurrent bleeding, complications,

and death were studied by recruiting 144 adults, aged 18 and up, with cirrhosis and esophageal variceal hemorrhage. Seventy-two patients were randomly assigned to each group. In one treatment arm, nadolol was initiated at a once daily dose of 80mg, and then adjusted over the following five days to decrease the baseline heart rate by 25%, but not below 55 bpm. After heart rate reduction and stabilization, isosorbide mononitrate (ISMN) was begun with a 20mg bedtime dose and, subsequently, increased to 40mg twice daily, or until side effects prevented further dosage increase. The other 72 treatment arm subjects received esophageal ligation using either a single band and an overtube device or using a multiband ligating device. A maximum of eight bands per session were placed at randomization date, on day seven, and each two to three weeks until eradication, or until each varix was too small to be banded. Endoscopy follow up was performed three months following randomization and at six month intervals thereafter. This RCT calculated a 49% rebleed rate for the EVL only group as compared to a 33% rebleed rate for the nadolol/ISMN treatment arm over a median follow up period of 21 months. Actuarial probability of survival was similar in the two groups at two years (P=0.52). Treatment complications, classified as severe occurred in 12% of the ligation arm, but in only 3% of the pharmaceutical arm (P=0.05). However, when the overall complication rate was assessed, the EVL group had a 31% complication rate as opposed to a 26% rate in the medication group (P=0.71).[18]

This literature search found one study, by de la Peña et al[19], which compared variceal ligation plus nadolol to EVL alone for variceal rebleeding prophylaxis. De la Peña et al.[19] enlisted 80 cirrhotic adults, aged 18-75 years, with esophageal or gastroesophageal varices for this randomized study conducted at four separate hospital

sites. Initially, all patients received emergency endoscopy EVL or endoscopic injection sclerotherapy (EIS) plus somatostatin at 250 micrograms/hour for five days. The variceal ligation arm patients were treated with multiband devices (the Six Shooter-Saeed Multi-Band Ligator and the speed band by a different maker). Ligation was started at the cardia or just inferior to it and repeated at 10 to12 day intervals until eradication. The EVL plus nadolol arm patients received a once daily oral nadolol dose, starting at 40mg daily, which was increased in dosage until a 25% decrease in resting heart rate was reached. Follow up was performed in both groups at 3-, 6-, and 12-month intervals, and then annually thereafter. Actual mean follow up was 15 +/- 8 months in the EVL group, and 17.5 +/- 7.8 months in the EVL plus nadolol group. The primary endpoint was variceal rebleeding. Several secondary endpoints were sought, among them, mortality rate, variceal eradication, recurrence rate of esophageal varices, complications of treatment in either protocol arm, or treatment failure. The rebleeding rate reported for those patients treated with the combination of EVL plus nadolol was 14% (6/43 pts), for ligation alone, 38% (14/37 pts). Mortality was similar in both groups, as was the median number of endoscopy treatments needed to achieve variceal eradication (three; range one to seven). The benefit of nadolol adjuvant to EVL therapy was observed when the probability of variceal recurrence was calculated for the first year following treatment. Varices reappeared after eradication in 54% of the EVL plus nadolol group, as compared to a 77% recurrence rate in the EVL alone treatment group (P=0.06, log rank test). Additionally, researchers saw a trend towards fewer EVL sessions to treat new varices in the combined therapy group.[19]

Two studies using transesophageal intrahepatic portosystemic shunt (TIPS) were reviewed. The first, a randomized control trial by Pomier-Layrargues et al[5], published in 2001, compared the variceal rebleeding and two year survival rates in moderate to severe cirrhotic patients treated with esophageal variceal ligation (EVL) as opposed to TIPS. The variceal rebleeding rate at two years with TIPS was 18.5% versus 66% with EVL ($p<0.001$) for 80 patients, aged 18-75 years, with cirrhosis and an episode of variceal hemorrhage. Nine variceal rebleeding events occurred in 8/41 (19.5%) patients in the TIPS arm due to stent stenosis and stent thrombosis. Variceal bleeding occurred 30 times in 22/39 patients in the EVL group (56.4%). Uncontrolled rebleeding occurred in 11 patients in the ligation group (eight were rescued by emergency TIPS) but there was no evidence of uncontrolled rebleeding in the TIPS group. Study authors concluded that TIPS significantly reduced the incidence of variceal rebleeding but did not increase the survival rate at two years when compared to variceal band ligation. Since TIPS intervention is associated with an elevated incidence of hepatic encephalopathy, notation was made in this study that seven patients in each arm of the study had encephalopathy on the day of randomization. During the follow up period (mean 20.9 months) the cumulative probability of developing encephalopathy at two years from date of study inclusion was not significantly different between groups (47% TIPS vs. 44% EVL).[5]

A separate TIPS-related study, this one by Sauer et al[20], compared TIPS to EVL plus propranolol. Eighty-five cirrhotic adults, aged 31-87, with a single episode of acute esophageal variceal bleeding were enrolled into this long-term randomized control study. Primary endpoints compared recurrence of variceal bleeding, and secondary endpoints were death from any cause and encephalopathy. The mean study length was 4.1 years in

the TIPS group, and 3.6 years in the EVL arm. All patients with initial active variceal bleeding were treated with injection sclerotherapy using 5% ethanolamine oleate and subsequently underwent either the TIPS or EVL treatment protocol within 48 hours. TIPS arm subjects had stents dilated to 8-12mm and the portal venous pressure gradient was titrated to between 10 to15mmHg until the disappearance of variceal or collateral vessel perfusion in the portogram occurred. After stent placement, continuous IV heparin was given for three days along with mezlocillin and metronidazole broad-spectrum antibiotic prophylaxis. The patients undergoing endoscopic ligation in this study had multiple-band ligation sessions every one to two weeks until variceal eradication or until the varices were reduced in size and too small to be treated by ligation. EVL therapy was augmented with twice daily oral doses of propranolol, starting at 40mg/day, and increased by 40mg/day, until resting heart rate was reduced to 75% of baseline. All study participants were followed up at three month intervals during the first year after enrollment, at six month intervals during the second year, and annually thereafter.[20]

Sauer et al.[20] were successful in all TIPS shunt placements and in complete variceal eradication for all 43 TIPS-arm patients. Rebleeding of varices occurred in 7/43 (16.3%) of the TIPS arm patients. In the EVL+ propranolol group, after a mean of 3.6 endoscopic ligation sessions, taking approximately two months to complete, varices were obliterated in 37/42 (88%) of the patients and rebleeding occurred in 10/42 (23.8%). Researchers did not find the difference in the probability of esophageal rebleeding to be statistically significant. The cumulative death rate for the TIPS arm was 24.1% and in the EVL group it was 17.8%. Both groups had higher rates of death in patients with more advanced liver disease, specifically, Child C patients. During the study period, the

calculated probability of encephalopathy was 40.5% in the TIPS arm and 20.5% in the EVL arm ($P<0.05$), and the analysis by Cox regression proved the Child-Pugh class and treatment arm were independent predictors for encephalopathy.[20] Researchers concluded that, due to the beneficial efficacy and lower costs of treatment, endoscopic ligation therapy plus propranolol has use as the initial treatment for the prevention of recurrent variceal bleeding, whereas TIPS treatment should be reserved for rescue therapy after endoscopic and pharmacological treatments have been tried.

DISCUSSION

Studies regarding esophageal variceal rebleeding rates are cumbersome to compare for many reasons. First, ethical limitations must be first and foremost in the researchers' minds as they design a study. Every trial design, in the face of an acute, and potentially life threatening esophageal bleed, must deliver what we know to be leading-edge quality patient care and must not compromise the extension or quality of life for the sake of scientific experimentation.

Secondly, variceal rebleeding study comparison is made challenging by the variety and nuances of measured endpoints. For instance, prevention of recurrent variceal bleeding (secondary)[17, 20] was measured in several studies and prevention of primary variceal bleed was measured in others.[3, 22] Variceal bleeding was both a primary and secondary endpoint, as was any rebleeding, defined commonly as any episode of (GI) hematemesis or melena (or both) occurring during follow-up, as well as any "significant bleeding" which was defined differently by each study group. The incidence of side effects or complications of therapy were detailed in some studies, but not all, and each

study picked those side effects or complications they felt were important to follow, again making it difficult to compare studies across the board.

Thirdly, the variety of therapeutic modalities used as comparisons to variceal ligation, be it vasoactive medications, EIS, or TIPS, created seemingly endless opportunities for study. The difficulty in creating gold-standard randomized and blinded studies lies in the sheer number of viable options available, as well as in the impossibility of blinding such disparate therapies. Propranolol, nadolol, timolol, isosorbide mononitrate, octreotide, vasopressin, and omeprazole[8], to name a few, have all been used, alone or in combination, as pharmacological interventions in the studies found in this literature search. Additionally, pharmacological agents were used as adjuvants to both endoscopic band ligation[6], and to injection sclerotherapy.[3]

Control of variceal rebleeding was achieved using multiple methods introducing confounding factors into the studies, thus reducing the ability to assess intervention effectiveness. For example, Sauer et al.[20] tested the effectiveness of EVL plus propranolol against TIPS therapy; if active bleeding occurred after endoscopic validation of esophageal varices, the patient underwent a balloon tamponade procedure and/or intravenous octreotide for 48 hours. Likewise, Sarin et al. (2005) controlled rebleeding in both the EVL and the drug therapy study arms with vasoactive drugs using either terlipressin or somatostatin. A study by Villanueva et al. (2001) compared EVL to nadolol plus ISMN, and treated patients with rebleeding varices with somatostatin, emergency sclerotherapy, or both. In all three studies, rebleeding patients received emergency intervention, however, it is not apparent which, or how many, treatments they received. In the Romero et al. (2006) study, which compared beta-blocker plus ISMN

against EVL plus sclerotherapy, all rebleeding patients were treated with injection sclerotherapy, but in doing so added a confounding factor to the pharmacological treatment arm. In contrast, the study conducted by Pomier-Layrargues et al. (2001) treated variceal rebleeding by shunt revision (dilatation and/or addition of new stents) in the TIPS group, and treated the ligation group with additional banding. Likewise, de la Peña et al. (2005) addressed active rebleeding rescue using the same treatment method to which the patients had been randomized. In reviewing these interventions, it is a reasonable assumption that the emergency treatments, if different than the treatment being analyzed, may skew study outcomes by masking true endpoint occurrences through the addition of new variables. While controlling rebleeding episodes is paramount, additional methods of bleeding control compound the difficulties in assessing which modality is affecting the change.

Trial design inconsistencies further complicated comparison of esophageal rebleeding studies. Sauer et al. (2002) chose to prophylactically treat the TIPS arm subjects with both IV heparin and broad-spectrum antibiotic therapies (mezlocillin and metronidazole) after stent placement. Patients receiving EVL plus propranolol therapy did not receive anticoagulant or antibiotic prophylaxis. Anticoagulant therapy can provoke rebleeding episodes, creating bias in the TIPS arm of the study, because of increasing rates of variceal bleeding, overall bleeding, and conceivably, death. The addition of prophylactic antibiotic medications may reduce mortality, thus favoring the TIPS arm patients by augmenting their immune systems, thereby increasing survival rates. Similarly, patients in the Romero et al. (2006) EVL treatment arm were medicated with sucralfate (1 gram four times daily), and followed with endoscopy at one, three, and

six month intervals after variceal eradication, and every six months thereafter throughout the treatment period. In contrast, subjects in the pharmacological treatment arm were followed with compliance monitoring visits every three months after reaching hemodynamic goal endpoints, but the study analysis did not indicate that this group received any further endoscopy or sucralfate. Since endoscopy may result in mucosal tears or hemorrhage and esophageal perforation, the subjects in the EVL treatment arm may be predisposed to an increased rate of esophageal bleeding, overall bleeding, and mortality. The addition of sucralfate to the ligation group, but not to the pharmacological group, could create a reverse bias effect by decreasing esophageal mucosal lining irritability and likelihood to bleed. Studies that include disparate variables and unequal treatments, such as those described above, reduce the ability to link cause and effect and hence, study validity.

The duration of studies in the published literature differed markedly, providing potential for the data to be misunderstood, and resulting in an incorrect analysis. Given the high rate of patient mortality in the immediate three month to one year follow-up after an index bleed, study length has a huge impact when considering data analysis regarding long-term treatment efficacy, side effects, complications, morbidity, and mortality. One pharmacological study reviewed had a two week gastroscopy follow up that only 69% of the patients submitted to.[8] Another study, involving 324 patients, dosed subjects with vasoactive medications for only 72 hours, and had established the study duration as the hospital stay only, due to a large percentage of study subjects who lived in remote areas and were lost to follow up[6]. These studies are well executed, and valid in their own right, but cannot truly be compared side-by-side with trials that have a longer duration of study.

The shortest study length included in this review was 11.8 months. A number of variceal rebleeding studies with a shorter duration were excluded because they did not target long-term variceal rebleeding prevention.

Likewise, choices of inclusion and exclusion criteria regarding patient populations were significantly variable. While five of six of the included studies specified only cirrhotic patients, Sarin et al (2005) included and compared study results with patients suffering from cirrhosis and noncirrhotic portal hypertension. Sauer et al. (2002) included 12 patients with a history of previous variceal bleeding which had occurred at least six months prior to the index bleed, but had not received any medical or endoscopic treatment. The remaining 73 patients in this study had a history of only the index bleeding episode, which is more consistent with inclusion criteria in the comparative studies. One excluded study included patients as young as 16 years of age, while most trials included only patients18 years and up. As studies quantify and measure death and comorbidities, this age difference may produce an age-biased result, both, because the subject has not had the disease state for as long a time and, secondly, they may be healthier overall, due to their youth. Some trials measured outcomes in only alcoholic cirrhotic patients[4], whereas others included any type of cirrhosis, whether it was induced by virus, Wilson's disease, autoimmune etiology, primary biliary cirrhosis, Budd-Chiari syndrome, or cryptogenic in nature.

Of the six studies, two were performed at more than one clinical site. The de la Peña et al. (2005) study was a multicenter trial conducted at four sites, while the Romero et al. (2006) study took place at two facilities. Having consistency at separate sites, regarding: (1) controls, (2) definitions of events, or (3) choice of intervention, requires

greater oversight and coordination than simply designing the trial around one location. Pomier-Layrargues et al. (2001) specifically conducted their study as a single-center trial "to avoid bias that may result from the differences in technical expertise in different centers and also to control for the accuracy of critical information such as (rates of) rebleeding, occurrence of encephalopathy, and cause of death."[5]

As these studies are of a highly varied nature, it creates a quagmire of data. While ultimately likely to be of use in the pursuit of more effective therapy, such data is difficult to wade through to extract the necessary information required to make fully informed, non-biased decisions regarding the best and most appropriate care available for each individual.

The included randomized controlled trials of esophageal variceal ligation compared to other therapies are seen in Table II. Five of the six trials maintained one arm of the study solely using esophageal variceal ligation, helping to compare like studies. (The sixth, Sauer et al[20], augmented the use of EVL with twice daily doses of propranolol, then compared that combination therapy to TIPS, to assess whether the addition of a beta-blocker to ligation could improve EVL outcome in regards to prevention of secondary variceal bleeding, since no trials had yet measured this combination in a long-term study). As we can see in Table II, variceal rebleeding rates using EVL alone range between 7% and 56.4%, with death rates ranging from 8.5% to 42%, as compared to rebleeding rates of 9.3% to 36%, and death rates ranging from 11.6% to 41.5% for comparison studies. Except for the trial by Sarin et al. (2005) pairing EVL against propranolol plus ISMN, none of the other trials showed a benefit in the long-term prevention of variceal rebleeding by esophageal variceal ligation alone, as

compared to beta-blocker plus nitrate, EVL plus beta-blocker, or TIPS. The results showing TIPS to be more effective than EVL is not a surprise: studies have shown that transesophageal intrahepatic portosystemic stent treatment reduces the incidence of variceal rebleeding through a reduction in portal pressure, but does so at the risk of a greater incidence of encephalopathy, higher treatment costs, and without improvement in mortality.[11] However, why do the other four studies in this review result in variceal rebleeding data that do not seem to support the industry-accepted standard that has made EVL the treatment of choice for secondary prophylaxis of variceal rebleeding?

On closer examination, we see, of the three studies comparing solely variceal ligation therapy to pharmacological therapy, the study by Sarin et al (2005) claimed equal benefit between EVL and combination drug therapy, Romero et al (2006), likewise, reported no superiority of EVL over nadolol plus ISMN for the prevention of variceal rebleeding, while, in contrast, Villanueva et al.[18] showed a greater benefit with pharmacological treatment. The Sarin et al. (2005) report specified an equal benefit from both ligation and combination pharmacological therapy when applied to cirrhotic patients, but added that EVL is more effective in secondary variceal rebleeding when applied to patients with noncirrhotic portal hypertension. Villanueva et al.[18] reported a benefit with combination nadolol plus ISMN in both prevention of variceal rebleeding and a decreased complication rate. One explanation for these differences may be the study duration. The Sarin et al[17] study duration follow-up of 11.1 months in the pharmacological arm, and 12.4 months in the EVL arm, may lead us to misinterpret results. Band ligation therapy does not reduce portal hypertension, or the hepatic venous pressure gradient (HVPG), important to variceal rebleeding rate. Thus, esophageal

ligation results in known disadvantages of short-term effectiveness, accompanied by frequent variceal recurrence and rebleeding rates. It is reasonable, then, to extrapolate that a study of shorter duration may not be of sufficient length to capture the actual rebleeding or complication rates that may come with treatment, and which would increase the rebleeding rate of patients treated ligation therapy, possibly changing study outcome. Additionally, the study by Sarin et al.[17], comparing EVL to propranolol plus ISMN, had the highest percentage of Child's class A patients than any of the other studies by far (the average percentage of patients in Child classification A for both arms of this study is 45.5%, as compared to the overall average of 24.4% Child A subjects in the other studies combined). A disproportionate amount of Child A subjects in a study decreases the overall severity of liver disease in that patient population, which, in turn, decreases the likelihood of variceal rebleeding and increases the patient's one- and two-year survival rate. A last consideration is that Sarin et al.[17] included both cirrhotic and noncirrhotic patients (73.7 and 26.3%, respectively), as opposed to every other study reviewed here, which included only cirrhotic populations. Inclusion of noncirrhotic subjects decreases the risk of variceal rebleeding for this selected population because liver function is better preserved in noncirrhotic patients, thereby translating to a reduction in variceal bleeding rate for the overall study results.

The randomized control trials by Romero et al.[15] and Villanueva et al.[18] both compared EVL to nadolol plus isosorbide mononitrate (ISMN) and resulted in lower rates of variceal rebleeding and death among subjects in the pharmacological arm of the studies. These two studies reported pharmacological variceal rebleeding rates between 28% and 36%, and death rates from 21.2% to 32%, as opposed to higher rates of variceal

rebleeding and death rates with variceal ligation (40% to 44%, and 46% to 49%, respectively). Romero et al.[15] did not find any advantage in EVL over pharmacologic therapies, and used lower dosages of medications: 88mg± 68mg of nadolol daily and 57.7mg ± 27mg ISMN. In comparison, the study by Villanueva et al.[18], which used a mean dose of 96mg ±56mg nadolol per day, augmented by a mean dose of isosorbide mononitrate at 66mg±22mg per day, concluded that combination therapy is more effective than endoscopic ligation for the prevention of recurrent bleeding and associated with lower rates of major complications. Sarin et al.[17] may also have achieved lower rebleeding rates and death rates than either of these studies secondary to their use of higher dosages of beta-blocker (mean propranolol dose 109mg±46mg per day) and nitrate (mean dose of ISMN was 34.2mg±11.7mg per day).

Another explanation could be the advent of a new therapeutic standard as a result of combining previously accepted treatment modalities. The RCT by de la Peña et al.[19] showed nadolol plus variceal ligation to be significantly more effective at reducing the incidence of variceal rebleeding and reducing overall upper GI bleeding, when compared to EVL therapy alone, but that it did not significantly change mortality rate. By combining a beta-blocker, to reduce portal blood flow, and ligation, which results in a reduction of rebleeding, complications, and deaths, as compared to endoscopic sclerotherapy[11], and which does not carry the higher attendant risk of encephalopathy that TIPS or portocaval shunt surgery do, this pairing may optimize patient outcomes without increasing the incidence of variceal rebleeding, overall upper GI hemorrhage rate, complications, or contraindications.

This benefit of combined therapy seems to be substantiated by the remaining study comparing variceal ligation plus propranolol, another nonselective beta-blocker, to TIPS therapy. As we can see in Table II, variceal rebleeding rates using EVL ranged between 7% and 56.4%, with death rates ranging from 8.5% to 42%. The study by Sauer et al.[20], marrying EVL with propranolol, falls somewhere in the middle, with a variceal rebleeding rate of 23.8%, and a death rate of 17.8%. Upon closer inspection, Sauer's 23.8% variceal rebleeding rate is one the lowest EVL-induced variceal rebleeding rates, with the exception of the study results by Sarin et al.[17] (7%) and by de la Peña et al.[19] (9.3%), both of which are rebleeding rates for EVL combined with nadolol, a different beta-blocker. The important thing to observe is that the rebleeding rate by Sarin et al.[17] of 7% using EVL in isolation, was achieved with the factors listed above, and that the variceal rebleeding and death rates by Sauer et al.[20] were accomplished with the longest follow-up period, 43.2 months, a more balanced Child's classification patient profile and use of a cirrhotic-only study population, adding import to use of ligation plus beta-blocker, and giving cause for further study of this combination therapy. Additionally, although the TIPS arm of the study by Sauer et al. (2002) did, in fact, have a significantly lower variceal rebleeding rate than the EVL plus propranolol arm (16.3% versus 23.8%, respectively) it also resulted in an increased mortality rate (24.1% versus 17.8%), which does not contradict other studies comparing TIPS and EVL. One must conclude, regarding the increased mortality associated with TIPs therapy, as shown with the study by Sauer et al.[20], it doesn't make sense to recommend a TIPS treatment protocol to a patient unless it is after safer treatments have been unsuccessful, as is current industry protocol.

The 2005 study by Pomier-Layrargues et al.[5], comparing EVL to TIPS, in a study of intermediate duration, showed a significant benefit from TIPS therapy in the reduction of variceal rebleeding and in overall upper GI bleeding rates. Additionally, it did not show any difference in mortality rate at two years, and, interestingly, did not show a significant difference in the rate of encephalopathy at two years between the two treatment modalities. It is unclear whether this study's use of only Child's B class patient population was instrumental in this lack of difference. One problem with comparing this study to the others is in the timing of treatments after control of the initial variceal bleeding and subsequent randomization. The study design required that the patient be hemodynamically stable for at least 24 hours after the initial bleeding episode was controlled, then randomization to separate treatment arms occurred. Ligation first occurred on day one after randomization, while TIPS procedure occurred within 72 hours. Since variceal rebleeding can occur as frequently as 30% to 50% within the first day of the acute episode[11] this difference in starting times for treatment arms may have had an effect on rebleeding rates and mortality rates.

RECOMMENDATIONS FOR FURTHER STUDY

As much as possible, studies on long term variceal bleeding prevention therapies will need to be performed in a uniform manner to equally facilitate therapy effectiveness and to equally measure the likelihood of side effect profiles and mortality.

LIMITATIONS OF STUDY

While the six studies provide a solid foundation for the evaluation of esophageal variceal ligation therapy, the inclusion of additional studies would help further assess whether EVL is the preferred treatment for the prophylaxis of variceal rebleeding. Several recent studies were unavailable for review, but based upon the abstracts, these studies would provide a valuable contribution to this evaluation. Additionally, all studies performed prior to 1999 were excluded because of technological and pharmacological advances; other studies were omitted because they were not available in the English language. However, due to these somewhat arbitrary constraints, valid trials may have been omitted.

CONCLUSION

Esophageal variceal ligation, alone, shows no superiority to treatment with beta-blocker and nitrate, or TIPS procedure, and is less effective than EVL plus nadolol in the prevention of variceal rebleeding. While the ideal option for primary or subsequent esophageal variceal bleeding would be safe and effective prophyllactic prevention, current treatments remain moderately efficacious and there remains the need for effective, safe, preventive therapeutic modalities after immediate emergency rescue treatment. Therapies such as endoscopic injection sclerotherapy (EIS) and TIPS are not effective as prophyllaxis, as the EIS-associated risk of bleeding and esophageal stricture, and increased rates of TIPS-associated hepatic encephalopathy and increased mortality are not logical if we keep in mind the patient's quality of life and reason for treatment. Therefore, because additional trials and advances in pharmacology are improving

treatment of increased portal hypertension, and technological improvements are occuring constantly, the combination therapy effect seems to be a reasonable direction for future study. These current trials do not support esophageal variceal ligation alone as the most efficacious treatment available, but rather indicate that ligation may be improved when used with a beta-blocker. An approach which promotes secondary prophylaxis of variceal rebleeding through pharmacological therapy and concurrent endoscopic ligation, seems promising and necessary. The evidence remains controversial regarding the effectiveness of variceal ligation therapy when used in isolation; however, there is strong evidence of therapeutic improvement when ligation is augmented by beta-blocker therapy.

Table I: Literature Review

Author/title/ Journal	Year Pub-lished	Patients/ Population	Intervention	Comparison	Outcome(s)	Study Type	Validity (Jadad Score)	Comments
2/Sarin, S., Wadhawan, M., Gupta, R., Shahi, H./ Evaluation of endoscopic variceal ligation (EVL) versus propanolol [sic] plus isosorbide mononitrate/nadolol (ISMN) in the prevention of variceal rebleeding: Comparison of cirrhotic and noncirrhotic patients[17]/ Digestive Diseases and Sciences	2005	137 cirrhotic or noncirrhotic patients with proven esophageal varices as the bleeding source on endoscopy.	Endoscopic variceal ligation every 2 weeks until variceal obliteration versus propranolol plus ISMN	Bleeding versus no bleed	EVL arm 14.1% rebleed rate versus 27.2% drug therapy arm rebleed rate. EVL more effective than drug therapy in patients with noncirrhotic portal hypertention (NCPH), but equally effective in cirrhotic patients.	RCT	J = 3	Mean follow up 11.8mos.
13/de la Pena et al/ Variceal ligation plus	2005	80 cirrhotic adults, aged 18-75, with	Esophageal variceal ligation	Primary endpoints variceal	Rebleeding rate EVL + nadolol =14% (6/43	RCT, not blinded	J=3	Mean f/up 15 +/_ 8mos in EVL

Key: EVL: esophageal variceal ligation; ISMN: isosorbide mononitrate or 5-isosorbide mononitrate; NCPH: noncirrhotic portal hypertension; TIPS: transesophageal intrahepatic portosystemic stent

Table I: Literature Review

Author/title/ Journal	Year Pub-lished	Patients/ Population	Intervention	Comparison	Outcome(s)	Study Type	Validity (Jadad Score)	Comments
nadolol compared with ligation for prophylaxis of variceal rebleeding: a multi center trial[19]/Hepatology		esophageal varices or esophago-gastric type gastroesophageal varices.	(EVL) alone, versus EVL with daily oral nadolol	rebleeding or not. Several secondary endpoints.	pts), for EVL alone 38% (14/37 pts)			group, 17.5+/- 7.8 months in EVL+ nadolol group. Study performed at four sites.
14/Romero et al/ Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled	2006	109 cirrhotic patients with a recent variceal bleed	Once daily oral nadolol titrated upwards until 25% reduction HR or until 55 bpm. Then daily BID 5-ISMN added. In EVL group, banding @ 2wks until eradication.	GI and variceal rebleeding or not were the primary endpoints.	No differences in variceal rebleeding (40% versus 36%) in nadolol+5-ISMN and EVL groups, respectively.	RCT	J=3	Mean follow up 17 and 19 months in nadolol+5-ISMN and EVL groups, res-pectively. Study per-formed at two sites.

Key: EVL: esophageal variceal ligation; ISMN: isosorbide mononitrate or 5-isosorbide mononitrate; NCPH: noncirrhotic portal hypertension; TIPS: transesophageal intrahepatic portosystemic stent

Table I: Literature Review

Author/title/ Journal	Year Pub-lished	Patients/ Population	Intervention	Comparison	Outcome(s)	Study Type	Validity (Jadad Score)	Comments
trial[15]/ Alimentary Pharmacology & Therapeutics								
7/ Pomier-Layragues, G, et al/Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomized trial[5]/ Gut	2001	80 patients, aged 18-75 years, with cirrhosis and an episode of variceal hemorrhage .	Intrahepatic portosystemic stent(s) placed versus EVL.	Rebleeding incidence at 2 yrs was a secondary endpoint.	Variceal rebleeding rate at two years 18.5% with TIPS vs 66% with EVL.	RCT	J=3	Mean follow up 628 days (20.9mos).
8/Villanueva, C, et al/ endoscopic ligation compared with	2001	144 adults, aged 18 and up, with cirrhosis	EVL versus daily oral nadolol plus BID	Recurrent bleeding or no bleeding.	49% rebleed rate for EVL, 33% for medication	RCT	J=3	Median follow-up 21 months.

Key: EVL: esophageal variceal ligation; ISMN: isosorbide mononitrate or 5-isosorbide mononitrate; NCPH: noncirrhotic portal hypertension; TIPS: transesophageal intrahepatic portosystemic stent

Table I: Literature Review

Author/title/ Journal	Year Pub-lished	Patients/ Population	Intervention	Comparison	Outcome(s)	Study Type	Validity (Jadad Score)	Comments
combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding[18]/ The New England Journal of Medicine		and esophageal variceal hemorrhage.	isosorbide mononitrate		treatment.			
10/Sauer, P, et al/ Endoscopic variceal ligation plus propranolol vs. transjugular intrahepatic portosystemic stent shunt: a long-term randomized trial[20]/Endoscopy	2002	85 cirrhotic adults, aged 31-87, with single episode of acute esophageal variceal bleed.	EVL plus propranolol versus TIPS	Control of bleed.	EVL group 23.8% rebleed rate vs 16.3% rebleed rate for TIPS group.	RCT	J=3	Mean study length 4.1 yrs in TIPS group, 3.6 yrs in EVL group.

Key: EVL: esophageal variceal ligation; ISMN: isosorbide mononitrate or 5-isosorbide mononitrate; NCPH: noncirrhotic portal hypertension; TIPS: transesophageal intrahepatic portosystemic stent

Table II: Trials Comparing Esophageal Variceal Ligation versus Other Therapies

Author (year)	Treatments compared	n	Child A	Child B	Child C	Follow-Up (mo)	% Variceal Rebleeding	% Overall Rebleeding	Death Rate %
Sarin (2005) [17]	EVL	71	50	36	14	12.4	7	14.1	8.5
	Propranolol + ISMN	66	41	42	17	11.1	22.7	27.2	6.1
Romero (2006) [15]	EVL	52	32	58	10	19	40	46	19.2
	Nadolol + ISMN	57	40	44	16	17	36	47	21.2
Villanueva (2001) [18]	EVL	72	15	60	25	22	44	49	42
	Nadolol + ISMN	72	26	54	19	20	28	33	32
De la Peña (2005) [19]	EVL	37	16	54	30	15	27	38	10.8
	EVL + Nadolol	43	14	58	28	17.5	9.3	14	11.6
Pomier-Layrargues (2005) [5]	EVL	39	0	100	0	19.4	56.4	79	41.0
	TIPS	41	0	100	0	22.6	19.5	34	41.5
Sauer (2002) [20]	EVL + Propranolol	42	24	45	31	43.2	23.8	NR	17.8
	TIPS	43	35	37	28	49.2	16.3	NR	24.1

Key: EVL: esophageal variceal ligation. ISMN: isosorbide mononitrate. TIPS: transesophageal intrahepatic portosystemic shunt

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